IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants:	Harriet L. Robinson, Ellen F. Fynan, Robert G. Webster and Shan Lu		
Application No.:	08/187,879	Group:	1633
Filed:	January 27, 1994	Examiner:	Ngugen

For: IMMUNIZATION BY INOCULATION OF DNA TRANSCRIPTION UNIT

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BRIEF ON APPEAL

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Assistant Commissioner for Patents
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Sir:

This Brief on Appeal is submitted pursuant to the Notice of Appeal mailed on August 30, 2000 and received in the U.S. Patent and Trademark Office on September 5, 2000 in the above-referenced patent application. An Amendment After Final was faxed to the USPTO on January 29, 2001 with authorization to charge the fee for a three-month extension of time. An additional one-extension of time for submission of this Brief is requested. A Petition for Extension of Time and the appropriate fee are being filed concurrently with this Brief.

This Brief is submitted in support of the appeal of the Examiner's final rejection of Claims 44-46, 50, 51, 62-64, 68-70, 74 and 78-89 as set forth in the Office Action made final, which was mailed from the Patent Office on May 30, 2000.

Each of the requirements set forth in 37 C.F.R. § 1.192(c) follow under the separate headings.

I. Real Parties in Interest

The real parties in interest are the University of Massachusetts Medical Center (UMMC), 55 Lake Street North, Worcester, MA 01655 pursuant to an assignment by Harriet L. Robinson, Ellen F. Fynan and Shan Lu; St. Jude Children's Research Hospital (St. Jude), 332 North Lauderdale Avenue, Memphis, TN 38105, pursuant to an assignment by Robert G. Webster; and Pasteur Merieux-Connaught (Connaught), 58, Avenue Leclerc, 69007, Lyon, France, licensee of subject matter described in the subject application.

II. Related Appeals and Interferences

Appellants, the undersigned Attorney, Assignee and Licensee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. Status of Claims

As filed, the instant application contained Claims 1-56. Claims 8, 27 and 39 were canceled in a Preliminary Amendment filed on June 19, 1995. Claim 4 was canceled in an Amendment filed on February 7, 1996. Claims 57-80 were added in an Amendment filed on May 15, 1997. Claims 81-89 were added in an Amendment filed on March 4, 1998, and Claims 1-3, 5-7, 9-26, 28-38, 40-43, 52-61, 65-66, 73, and 75-77 were canceled in this same Amendment. Claims 47-49 and 71-72 were canceled in an Amendment filed on April 14, 2000. Claim 67 was canceled in an Amendment filed on January 29, 2001.

In summary, Claims 1-43, 47-49, 52-61, 65-67, 71-73, and 75-77 have been canceled. Claims 44-46, 50, 51, 62-64, 68-70, 74 and 78-89 are pending, and are the subject of this appeal.

IV. Status of Amendments

The Amendment after Final Rejection filed on January 29, 2001 has been entered, as indicated to Appellant's Attorney by Examiner Nguyen during a telephone conversation on February 23, 2001. The pending claims, as they stand upon entry of the Amendment after Final Rejection, are presented in the Appendix to this Brief.

V. Summary of Invention

Claims 44-46, 50, 51 and 89-89 are drawn to methods of immunizing a mammal against an immunodeficiency virus of interest, by administering a DNA transcription unit comprising DNA encoding an antigen of that immunodeficiency virus of interest operatively linked to DNA which is a promoter region, wherein the mammal is protected from disease caused by that immunodeficiency virus of interest. The immunodeficiency virus of interest is SIV or HIV, and the promoter can be of retroviral origin or not of retroviral origin. The DNA transcription unit can be administered by a variety of different routes of administration.

As described in the Specification at page 7, lines 5-8, "immunizing" as used in the claims refers to production of an immune response which protects, partially or totally, from the manifestations of infection (i.e., disease) caused by the infectious agent. Furthermore, immunizing can result in protection against infection, or infection to a lesser extent than would occur without immunization (page 7, lines 9-11). Thus, "immunizing" does not refer solely to protection against infection *per se* (although that is contemplated), but rather, refers also to generation of an immune response that lessens or eliminates manifestations of disease after infection with the infectious agent.

Claims 62-64, 68-70, 74 and 78-80 are drawn to compositions or plasmid vectors comprising one or more specific DNA transcription units comprising DNA encoding an antigen of the human immunodeficiency virus. The transcription units are described in detail in the Specification at page 45, line 16, through page 49, line 9.

VI. Issues

The claims stand rejected under 35 U.S.C. §112, first paragraph, as being non-enabled by the Specification. The following issues remain on appeal:

(1) Whether the Examiner erred in stating that the claims were not enabled in breadth and should be limited to constructs taught by Appellants;

(2) Whether the Examiner erred in stating that the claims were not enabled in breadth and should be limited to the routes of administration demonstrated by Appellants or known in the art to be effective for DNA vaccination;

(3) Whether the Examiner erred in stating that it was unclear whether protection was realized in the data presented; and

(4) Whether the Examiner erred in stating that the animal model used to generate the data was not correlatable to a model for determining vaccination strategies.

VII. Grouping of Claims

With respect to the issues on appeal, the claims do not stand or fall together. The claims fall into two categories: methods claims (Claims 44-46, 50, 51 and 81-89), and composition claims (Claims 62-64, 68-70, 74 and 78-80). Within the categories, Claims 44-46, 50, 51 and 81-89 stand or fall together, and Claims 62-64, 68-70, 74 and 78-80 stand or fall together.

VIII. Argument

A discussion of each of the issues for review is presented under a separate heading, in the order in which they were set forth above.

Issue 1

The Claims have been rejected under 35 U.S.C. §112, first paragraph because the Examiner contends that the breadth of the claims is non-enabled and that the claims should be limited to constructs taught by Appellants.

To be enabling under 35 U.S.C. §112, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. A specification which contains a teaching of how to make and use the full scope of the claimed invention must be taken as being in compliance with the enablement requirement of 35 U.S.C. §112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971).

The method claims (Claims 44-46, 50, 51 and 81-89) are drawn to methods of immunizing by administering a DNA transcription unit comprising DNA encoding an antigen of that immunodeficiency virus of interest operatively linked to DNA which is a promoter region.

The immunodeficiency virus of interest is SIV or HIV, and the promoter can be of retroviral origin or not of retroviral origin.

Such constructs and their preparation are described in detail in the Specification, particularly, for example, at p. 45, line 16 *et seq.* (Examples 11-15). Examples 11 and 13 describe methods for preparing constructs (both SIV-related and HIV-related), including specific constructs; Example 15 details how to clone additional sequences (e.g., *env* sequences) from patient isolates for use in preparation of additional constructs; and Example 12 describes testing of immunogenicity of the constructs. One of ordinary skill in the art, given these teachings of the Specification, would be able to generate constructs other than those specifically taught in the Specification for use in the methods of the invention.

The specific constructs taught in the Specification are representative of those useful in the methods. The use of the such constructs in the claimed methods is described, for example, in Example 14, which sets forth how to conduct a vaccine trial to assess efficacy of the constructs. One of ordinary skill in the art would understand that constructs other than these specific constructs could also be used in the methods of the invention, and would be able to assess the efficacy of such constructs. That is, one skilled in the art would accept the assertions in the specification as true and enabling, absent evidence to the contrary. There is nothing of record which might suggest that the guidance provided in the Specification would be insufficient to enable the skilled artisan to practice these claims. Accordingly, the specification enables one skilled in the art to make and use the claimed invention without undue experimentation.

With regard to the composition claims (Claims 62-64, 68-70, 74 and 78-80), these claims are drawn to compositions comprising a DNA transcription unit, or to vectors, wherein the DNA transcription unit or vector comprises a construct selected from the group consisting of: pCMV/HIV-1-NL4-3.dpol, pCMV/HIV-1-HXB-2.env, pCMV/HIV-NL4-3.env, JW4303/HIV-1-HXB-2.sgp120, and JW4303/HIV-1-HXB-2.sgp140. These constructs are the specific constructs described in detail in the Specification (see, e.g., page 45, line 16, through p. 49, line 9), and are fully enabled by the Specification. One of ordinary skill in the art, given the Specification, would be able to make these particular constructs without undue experimentation.

Issue 2

The Claims have been rejected under 35 U.S.C. §112, first paragraph because the Examiner contends that the breadth of the claims is non-enabled and that the claims should be limited to the routes of administration demonstrated by Appellants or known in the art to be effective for DNA vaccination.

The Specification describes a wide variety of routes that are suitable for DNA vaccination in the methods of the invention (see, e.g., p. 9, lines 11-21). The success of several routes can be seen, for example, in Example 4 (page 22, line 19 *et seq.*), where immunization by intramuscular, intravenous, and a combination of routes (intramuscular, intravenous, and intraperitoneal) provided excellent protection after challenge with disease; immunization by intranasal (mucosal) route provided good protection after challenge with disease; and immunization by intradermal or subcutaneous routes provided protection after challenge with disease that was superior to the control immunizations. In addition, gene-gun delivered DNA to the epidermis provided excellent protection after challenge with disease (see Example 6, page 28, line 8 *et seq.*).

Similar results were also obtained in the simian trial described in Example 14, the results of which are described in the Declaration under 37 C.F.R. §1.132 of Dr. Harriet L. Robinson (the "Data Declaration," submitted on March 1, 1996). It is noted that the Office Action dated May 30, 2000 acknowledges that the constructs described in the Data Declaration are the same as those disclosed in the Specification, as described in the Declaration under 37 C.F.R. §1.132 of Shan Lu, M.D., filed on April 14, 2000, although the constructs in the Data Declaration are described by a slightly different nomenclature (e.g., using the suffix 110 or 130) than those in the Specification (using the suffix 120 or 140, respectively). The results described in the Data Declaration were obtained not only with gene gun immunization but also with multiple-route immunization. Thus, one of ordinary skill in the art would understand that many different routes of administration can be used for the methods of the invention (Claims 44-46, 50, 51 and 81-89), and would be able to utilize a variety of routes in practicing the methods of the invention.

The composition claims (Claims 62-64, 68-70, 74 and 78-80) do not describe routes of administration of the compositions, and thus, this rejection is inapplicable to the composition claims. Even assuming *arguendo* that the rejection were applied to the composition claims, a variety of routes can be used to administer nucleic acid constructs and achieve protection against

disease, as discussed above. Therefore, one of ordinary skill in the art would be able to make and use these particular constructs without undue experimentation.

Issue 3

The Claims have been rejected under 35 U.S.C. §112, first paragraph because the Examiner contends that the claims are non-enabled in that it was not clear whether protection against disease was achieved. In the Office Action dated May 30, 2000, the Examiner states that it was not clear whether any level of protection was realized in the Data Declaration. The Examiner additionally states in the Office Action of May 30, 2000, that while the data demonstrated a reduction in viral load in the first 6 weeks following infection, the Specification does not support a method of reducing viral load, and that such a limitation would raise issues under 35 U.S.C. 101 as such a limited use would not rise to the level of a substantial utility. The Examiner further contends that the Specification "implies that a therapeutic response, hence an improvement in the disease manifestation of the patient" was necessary.

The experiments described in the Data Declaration relate to assessment of the ability of a nucleic acid vaccine to protect against disease in a highly virulent, uncloned SIVmac251 rhesus macaque model. The virus used generally causes $\geq$ 50% incidence of AIDS during the first year of infection (see, e.g., description of the virulence of the particular virus in Lu, S. *et al.,* "Simian Immunodeficiency Virus DNA Vaccine Trial in Macaques," *J. Virol. 70(6)*:3978-3991 (1996), a copy of which was submitted previously). In the case of highly virulent models, partial protection, rather than complete protection, against disease is usually expected.

As described in the Data Declaration, administration of nucleic acid constructs comprising pJW4303 vectors containing sgp110(120) or sgp130(140), resulted in a more rapid reduction of viral loads to chronic levels in the immunized animals following the subsequent challenge with the virus, in comparison to the rate of reduction in control animals (reduction was achieved in half the time). The ability of the vaccinations to effect such a rapid reduction of viral loads was particularly noteworthy in view of the virulence of the challenge virus. If a less virulent challenge virus were used, one of ordinary skill in the art would reasonably expect that even greater protection (e.g., further reduction of viral loads or other protective immune responses) would be achieved. Furthermore, if a smaller amount of challenge viruse were used

(e.g., the amount of virus tht would be present in a natural exposure, which is much smaller than the amount of virus used for the virus challenge during the vaccine trial), one of ordinary skill in the art would similarly reasonably expect that even greater protection would be achieved.

Thus, the data described in the Data Declaration do demonstrate immunizing and protection against disease, as those terms are used in the Specification and set forth in the methods claims (Claims 44-46, 50, 51 and 81-89). As indicated above, "immunization" refers to production of an immune response which protects, *partially or totally*, from the *manifestations of infection* (i.e., disease) caused by the infectious agent, and can result in protection against infection, or infection to a lesser extent than would occur without immunization. Thus, "immunizing" includes generation of an immune response that *lessens or eliminates* manifestations of disease when infection with the infectious agent occurs after immunization. Immunization that causes a rapid reduction in viral load (e.g., a reduction of viral load to the chronic level in 6 weeks instead of the average 12 weeks, as described in the Data Declaration) is consistent with the generation of an immune response that lessens manifestation of disease upon infection, and thus demonstrates "immunizing" as the term is described in the Specification.

Although the claims are not limited *per se* to methods of reducing viral load, Appellants disagree with the Examiner's position that a method of reducing viral load would raise issues under 35 U.S.C. §101 as lacking a substantial utility. The Utility Guidelines of the US PTO state that a "substantial utility" is a utility that defines a "real world" use. Rapid reduction of viral load clearly has a "real world" use, in that it reduces the window of time in which an individual has a high virus load, thus attenuating the acute phase of infection and thereby reducing transmission of infection. Such a reduction in transmission is particularly useful in a virulent model, such as the model used in the Data Declaration, where complete protection may not be expected (see, e.g., Lu *et al.*, *supra*, p. 3989, "Protection of a population as opposed to protection of the vaccinated individual"). Thus, a method of reducing viral load clearly presents a substantial utility.

It should be noted that a "therapeutic response" resulting in an "improvement in disease manifestation" as stated by the Examiner appears to imply a therapeutic treatment that occurs *after* infection. However, the methods of the invention are not drawn to *treatment*, but rather, to immunizing which results in protection against disease upon subsequent challenge by the

infectious agent. Rapid reduction of viral load is indicative of *a response which protects, at least partially, against manifestations of disease*, by attenuating the acute phase of infection. Thus, Applicants have demonstrated successful methods of immunization, as it is described in the Specification.

The composition claims (Claims 62-64, 68-70, 74 and 78-80) are drawn to constructs comprising antigens of HIV, including, for example, pCMV/HIV-1-NL4-4.dpol, JW4303.HIV-1-HXB-2.sgp120, and JW4303/HIV-1-HXB-2.sgp 140. These constructs and the other constructs are closely related to those constructs comprising antigens of SIV that are described in the Specification and in the Data Declaration (e.g., pSIV239.dpol, SIV239sgp110 or SIV239.sgp120, and SIV239sgp130 or SIV239sgp140), in that they utilize the same vectors (e.g., the pCMV or JW4303 vectors) and comprise portions of the env protein of their respective immunodeficiency viruses. One of ordinary skill in the art, understanding the close relationship between HIV and SIV and the similarity between the HIV-related constructs and the SIV-related constructs described in the Specification, would reasonably believe that similar protection against the manifestations of disease would be generated using the HIV-related constructs in humans, as were achieved using the SIV-related constructs in simians, particularly in view of the animal model used (as discussed in detail below).

Issue 4

The Claims have been rejected under 35 U.S.C. §112, first paragraph because the Examiner contends that the claims are non-enabled in that a correlation could not be drawn between the data presented relating to immunization against SIV, and results in humans for immunization against HIV. In particular, the Examiner states that the references cited by Applicants (i.e., Gardner, M.B., *Antiviral. Res. 15*:267-286 (1991); Gardner, M.B., *Dev. Biol. Stand. 72*:259-266 (1990); Johnson, P.R. and Hirsch, V.M., *Int. Rev. Immunol. 8*:55-63 (1992); and McClure, H.M. *et al., Ann. NY Acad. Sci. 616*:287-298 (1990)) with regard to the macaque model state only that the model is important for study of infection, and do not correlate to a model for determining vaccination strategies, so that the claims are not demonstrative of HIV vaccine effectiveness.

The references previously cited by Applicants were selected, in part, because they demonstrate the state of the art at the time the application was filed; they were further selected because of statements concerning the use of the models in development of vaccines. For example, the Gardner (1991) reference states:

> Animal lentivirus infections provide a valuable resource for understanding mechanisms of pathogenesis and for development of effective antiviral drugs and *vaccines* with direct relevance to HIV and AIDS (p. 268, Introduction, citations omitted and emphasis added).

This Gardner reference goes on to describe vaccine trials in the macaque model system (see page 269 *et seq.*). Thus, this Gardner reference clearly sets forth that animal lentivirus infections, such as SIV infection in macaques, are useful for development of vaccines, as exemplified by several studies using the SIV macaque model for vaccine trials.

As another example, the McClure reference states in its introduction:

> The magnitude and continuing growth of the current worldwide AIDS pandemic make the development of effective vaccines and antiviral drugs of utmost urgency. These efforts, especially studies of the pathogenesis of retroviral infections and testing of antiretroviral drugs, immune system modulators, and *vaccines* will be greatly facilitated by access to appropriate animal models. The SIV-infected nonhuman primate has been established as an excellent animal model system for conducting such studies. (p. 287, Introduction; citations omitted and emphasis added.)

Thus, the McClure reference specifically states that SIV-infected nonhuman primates are an excellent animal model system for studies which include studies of vaccines.

In view of these considerations, one of ordinary skill in the art, given the specification and the state of the art at the time the application was filed, as demonstrated by these references previously cited by Applicants, would find the macaque (SIV) model described in the specification and used in the Data Declaration to be an appropriate model that would be predictive for HIV vaccination. Thus, the methods claims (Claims 44-46, 50, 51 and 81-89) as they relate to immunizing against human immunodeficiency virus are fully enabled, and one of

ordinary skill in the art would be able to perform methods of immunizing against human immunodeficiency virus in the methods of the invention.

Furthermore, because one of ordinary skill in the art would find the macaque (SIV) model to be predictive for HIV, one of ordinary skill in the art would reasonably believe that the HIV-related constructs as presented in the composition claims (Claims 62-64, 68-70, 74 and 78-80), would be similarly useful as the SIV-related constructs were in the macaque (SIV) model. Thus, the Specification fully enables one of ordinary skill in the art would be able to make and use these particular constructs without undue experimentation.

Conclusion

In view of the discussion presented above, a variety of nucleic acid constructs, including the very specific constructs set forth in the composition claims, are enabled by the Specification, as are several different modes of administration of the constructs in the methods of the invention. Furthermore, the data previously presented demonstrates a protective response that was obtained in a well accepted animal model. Therefore, it is respectfully requested that the rejections be reversed and that the claims be allowed.

Respectfully submitted,

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APPENDIX

44. A method of immunizing a mammal against an immunodeficiency virus of interest selected from the group consisting of: simian immunodeficiency virus and human immunodeficiency virus, said method comprising administering to the mammal a DNA transcription unit comprising DNA encoding an antigen of said immunodeficiency virus of interest operatively linked to DNA which is a promoter region, in a physiologically acceptable carrier, wherein the DNA transcription unit is expressed in cells of the vertebrate, whereby the mammal is protected from disease caused by said immunodeficiency virus of interest.

45. The method of Claim 44, wherein the DNA transcription unit is administered in combination with one or more additional DNA transcription units, each comprising DNA encoding a different antigen of said immunodeficiency virus of interest operatively linked to a promoter region.

46. The method of Claim 45, wherein the antigens of the transcription units are from different subgroups of the immunodeficiency virus.

50. The method of Claim 44, wherein the immunodeficiency virus of interest is simian immunodeficiency virus.

51. The method of Claim 44, wherein the immunodeficiency virus of interest is human immunodeficiency virus.

62. A composition comprising a DNA transcription unit and a physiologically acceptable carrier, wherein the DNA transcription unit comprises DNA encoding an antigen of human immunodeficiency virus operatively linked to a promoter region, and wherein the DNA transcription unit comprises a construct selected from the group consisting of: pCMV/HIV-1-NL4-3.dpol, pCMV/HIV-1-HXB-2.env, pCMV/HIV-NL4-3.env, JW4303/HIV-1-HXB-2.sgp120, and JW4303/HIV-1-HXB-2.sgp140.

63. The composition of Claim 62, further comprising one or more additional DNA transcription units, each DNA transcription unit comprising DNA encoding an antigen of a different subgroup of the human immunodeficiency virus.

64. The composition of Claim 62, further comprising one or more additional DNA transcription units, each DNA transcription unit comprising DNA encoding an antigen of a different subtype of the human immunodeficiency virus.

68. A composition comprising more than one DNA transcription unit and a physiologically acceptable carrier, wherein each DNA transcription unit comprises DNA encoding an antigen of human immunodeficiency virus operatively linked to a promoter region, and wherein at least on of the DNA transcription units comprises a construct selected from the

group consisting of: pCMV/HIV-1-NL4-3.dpol, pCMV/HIV-1-HXB-2.env, pCMV/HIV-NL4-3.env, JW4303/HIV-1-HXB-2.sgp120, and JW4303/HIV-1-HXB-2.sgp140.

69. The composition of Claim 68, wherein each DNA transcription units comprises DNA encoding an antigen of Env protein from a different subgroup of human immunodeficiency virus.

70. The composition of Claim 69, wherein each DNA transcription unit comprises DNA encoding an antigen of Env protein from a different tissue tropism of human immunodeficiency virus.

74. The composition of Claim 68, wherein the DNA transcription unit comprises DNA encoding eight of the nine human immunodeficiency virus proteins.

78. A plasmid vector comprising a promoter region operably linked to a nucleotide sequence encoding an antigen of human immunodeficiency virus, wherein said vector comprises a construct selected from the group consisting of: pCMV/HIV-1-NL4-3.dpol, pCMV/HIV-1-HXB-2.env, pCMV/HIV-NL4-3.env, JW4303/HIV-1-HXB-2.sgp120, and JW4303/HIV-1-HXB-2.sgp140, and wherein said antigen of human immunodeficiency virus is expressed in a cell of a mammal inoculated with said plasmid vector.

79. The plasmid vector of Claim 78, wherein said antigen of human immunodeficiency virus is Env protein.

80. The plasmid vector of Claim 78, wherein said antigen of human immunodeficiency virus includes eight of the nine human immunodeficiency virus proteins.

81. The method of Claim 44, wherein the promoter region of the DNA transcription unit is not of retroviral origin.

82. The method of Claim 44, wherein the promoter region of the DNA transcription unit is of retroviral origin.

83. The method of Claim 44, wherein the DNA transcription unit is administered to a mammal through a route of administration selected from the group consisting of: intravenous, intramuscular, intraperitoneal, intradermal and subcutaneous.

84. The method of Claim 44, wherein the DNA transcription unit is adminnistered to a mammal by contacting the DNA transcription unit with a mucosal surface of the mammal.

85. The method of Claim 84, wherein the mucosal surface is a respiratory mucosal surface.

86. The method of Claim 85, wherein the respiratory mucosal surface is a nasal mucosal surface.

87. The method of Claim 85, wherein the respiratory mucosal surface is a tracheal mucosal surface.

88. The method of Claim 44, wherein the DNA transcription unit is microsphere-encapsulated.

89. The method of Claim 44, wherein the DNA transcription unit is administered parenterally to a mammal.